## REMARKS

Applicants acknowledge the current status of the claims, as reported in Office Action dated 18 August 2006. Claims 1-13 are pending; restriction of the claims has been made final and claims 12 and 13 are withdrawn from consideration; and claims 1-11 are under consideration. Reconsideration and allowance of the application in light of the foregoing amendments and the following remarks are respectfully requested.

Claims 4 and 8 are amended such that the term "or antigen binding fragment thereof" has been deleted. These amendments are supported by the specification as filed, and do not add new matter.

Claims 4, and 5 are also amended such that they depend from "any one of claims 1, 2 or 3" respectively. Claim 8 is also amended such that it depends from "any one of claims 6 or 7". Applicants assert these amendments: are supported by the application as filed; are obvious on their face; do not add new matter; do not alter the scope of the claimed subject matter; and are made for reasons unrelated to patentability, but for the purpose of style, grammatical structure, and readability of the claims.

***Information Disclosure Statement***

Applicants acknowledge the Examiner's consideration in full of Applicants' information disclosure statement and entry of the same.

***Specification***

In the office action at page 3, the Examiner has indicated that the various non-provisional US applications disclosed in the specification should be updated with their current status. Applicants have reviewed the specification and, to the best of Applicants' knowledge, the current status of the various non-provisional US applications disclosed in the specification are up to date. Applicants will continue to update the status of the various applications as necessary.

In the office action at page 4, the Examiner has indicated that the various trademarks disclosed in the specification should be capitalized and should be accompanied by the generic terminology. Applicants have reviewed the specification and, to the best of Applicants' knowledge, the trademarks disclosed in the specification are capitalized and are accompanied by the generic terminology. Applicants respectfully request the Examiner to bring to Applicants' attention any trademarks that are not capitalized or accompanied by generic terminology.

In the Office Action, at page 4, the Examiner suggests a new title for the present application. Applicants respectfully request consideration of a new title to be held in abeyance, until final disposition and allowance of the claims in the present application.

***Claim Objections***

In the office action at page 4, the Examiner has objected to Claims 1-11 as being drawn to non-elected inventions and has requested appropriate correction. Applicants respectfully request the requirement to amend the claims such that they are not drawn to non-elected inventions be held in abeyance, until allowable subject matter has been determined.

In the office action at page 4, the Examiner has objected to claim 4 under 37 CFR 1.75 (c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Specifically, the Examiner asserts that claim 4, which depends from claim 2, does not incorporate the CDR3 amino acid substitutions of base claim 2, thus does not further limit the subject matter of previous claim 2. Applicants respectfully disagree.

In the method of claim 2 the human antibody, or an antigen-binding fragment thereof has the following characteristics:

a) dissociates from human TNFα with a $K_{off}$ rate constant of $1 \times 10^{-3}$ $s^{-1}$ or less, as determined by surface plasmon resonance;

b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

Therefore, the antibody, or antigen binding fragment, of claim 2 comprises heavy and light chain CDR3 domains of specific amino acid sequence or, comprises heavy and light chain CDR3 domains wherein the specific amino acid sequence has been modified. The antibody in the method of claim 4, is D2E7, which is Applicants' most preferred embodiment (see specification page 15, lines 2-5). D2E7 has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, and has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4. Claim 4 incorporates all the limitations of claim 2 and further limits the antibody to a specific antibody, D2E7. In view of the

foregoing, Applicants respectfully request withdrawal of the objection to claim 4 under 37 CFR 1.75 (c) as being of improper dependent form for failing to further limit the subject matter of a previous claim.

***Claim rejections under 35 USC §112 first paragraph***

In the Office Action, at page 5, claims 4, and 8-11 are rejected under 35 USC §112 first paragraph, because the specification does not enable one skilled in the art to which it pertains to use the invention. Specifically, the Examiner asserts that the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description. Applicants respectfully disagree.

Applicants have disclosed, and one of ordinary skill in the art will recognize, that D2E7 is also referred to as HUMIRA® and adalimumab (see specification page 15, line 5). HUMIRA® is well known in the art and readily available to the public. Furthermore, Applicants have provided sufficient guidance with respect to the amino acid sequence of the variable heavy and variable light chains of D2E7. One of ordinary skill in the art can easily make D2E7 using recombinant molecular biological techniques. Contrary to the Examiner's assertion, a deposit of the antibody D2E7, or a cell line that produces the antibody D2E7, is not required for one of ordinary skill in the art to practice Applicants' claimed method.

In the Office Action, at page 8, claim 2, is rejected under 35 USC §112 first paragraph, as containing subject matter not described in such a way as to enable one skilled in the art to make or use the invention commensurate with the scope of the claim. Specifically the Examiner asserts that the specification only discloses anti-human TNFα antibodies, and antigen binding fragments thereof that comprise all six CDRs, three from heavy chain and three from light chain of D2E7, and the specification does not teach or provide examples of anti-human TNFα antibodies that comprise mutant CDR3 regions of antibody D2E7 and do not comprise the heavy and light chain CDR1 and CDR2 regions from the D2E7 for clinical treatment of anemia related to rheumatoid arthritis. Applicants respectfully disagree.

In the method of claim 2 the human antibody, or an antigen-binding fragment thereof has to meet the following characteristics:

a) dissociate from human TNFα with a $K_{off}$ rate constant of $1 \times 10^{-3}$ $s^{-1}$ or less, as determined by surface plasmon resonance;

b) have a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

c) have a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

The Examiner cites Paul, Fundamental Immunology, 3rd Edition, 1993, pp.292-295; and asserts that the formation of an intact antigen-binding site of antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consist of three CDRs, and provide the majority of the contact residues for the binding of the antibody to its target epitope. Applicants respectfully submit that the state of the art in recombinant antibody technology has changed significantly since 1993. Applicants assert the fact that not all of the CDRs of the antigen binding site may be necessary (or even utilized) in binding a specific antigen, and that functional antibody fragments comprising fewer than all 6 CDRs is well known by practitioners skilled in the art. In the specification as filed, on page 7, lines 5-12, Applicants teach and disclose examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) Nature 341:544-546 ), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR). Not withstanding the foregoing, no matter how many CDRs the binding fragment contains, the antibody or antigen binding fragment must dissociate from human TNFα with a $K_{off}$ rate constant of $1 \times 10^{-3}$ $s^{-1}$ or less, as determined by surface plasmon resonance.

The Examiner cites Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79(6):1979-1983, March 1982) and asserts that even minor changes in the amino acid sequence of the heavy and light chain variable regions may dramatically affect antigen binding function. The Examiner further asserts that the applicants have not provided sufficient guidance in the specification, there are no working examples, and undue experimentation would be required to practice the claimed therapeutic method. Applicants respectfully disagree.

The MPEP §2164.06 in relevant part provides that:

> The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not

> be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. United States v. Telectronics Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989).

It is also recognized that:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling).

MPEP §2164.08(b)

As stated above, the antibody or antigen binding fragment of method of claim 2 must not only have specific heavy and light chain CDR 3 sequences, but must also dissociate from human TNFα with a $K_{off}$ rate constant of $1 \times 10^{-3}$ $s^{-1}$ or less, as determined by surface plasmon resonance.

Applicants submit that the teachings of the specification and the knowledge in the art are commensurate with the scope of the claims, and one of ordinary skill in the art would not have to perform undue experimentation to perform the methods of the invention. The specification teaches at page 14-19 that heavy and light chain CDR3 domains play an important role in the binding specificity/ affinity of an antibody for an antigen and that the CDR3 domains of the light and heavy chain sequences of the antibody D2E7, *i.e.*, those CDRs recited in the claim, have advantageous properties for use in the invention. The specification describes not only the sequences of the light and heavy chain CDR3 domains, but also various substitutions which may be made within the CDR3 domains such that the CDR3 domain retains its high affinity binding characteristic. The instant specification also references U.S. Patent No. 6,090,382 (see, for example, page 15, line 6) which characterizes the CDR3 domains of SEQ ID NOs: 3 and 4.

In contrast to the Examiner's assertion, one of ordinary skill in the art would know how to make the antibodies, and antigen-binding portions thereof, described in the claims. The specification describes methods for making and expressing antibodies, and antigen-binding portions thereof, for use in the methods of the invention at pages 10-13. In addition, methods for making and expressing antibodies and antigen-binding portions thereof used in the invention were known in the art. Thus, in view of the fact that the CDR3 sequences described in claim 2, are described in the specification and known in the art as having high affinity for human TNFα, and that one of ordinary skill in the art would know how to make antibodies, or antigen-binding portions thereof, commensurate with the claims. In addition, as stated above the quantity of experiments is not determinative for 'undue experimentation'. One of ordinary skill in the art will recognize that the amount of experimentation needed is routine and by no means undue. Thus, Applicants' disclosure, in combination with the state of the art at the time of the invention, enables one of skill in the art to perform the methods of the claimed invention without undue experimentation.

In view of the foregoing amendments and remarks, Applicants respectfully request withdrawal of the rejection of claim 2 under 35 USC §112 first paragraph.

***Claim rejections under 35 USC §102)***

In the Office Action, at page 13, the Examiner has rejected claims 1-11, under 35 USC §102(b) as being anticipated by Salfeld et al (WO 97/29131) in view of http://www.emedicinehealth.com/rheumatoid_arthritis/article_em.html. The Examiner asserts that Salfeld et al., teach a method of treating rheumatoid arthritis, and since anemia is a common complication of rheumatoid arthritis, treatment of rheumatoid arthritis would necessarily treat anemia related to rheumatoid arthritis and thus Salfeld anticipates Applicants' claimed invention. Applicants respectfully disagree.

35 U.S.C. §102, in relevant part, states that:

> A person shall be entitled to a patent unless –
> the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Applicants' invention, is directed to a method of treating anemia in a patient by administering a therapeutically effective amount of a human antibody, or an antigen-binding fragment thereof, to the subject, wherein the antibody dissociates from human TNFα with a $K_d$ of 1 x $10^{-8}$ M or less and a $K_{off}$ rate constant of 1 x $10^{-3}$ $s^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an $IC_{50}$ of 1 x $10^{-7}$ M or less, such that the anemia is treated. In a further embodiment, the anemia in the patient is selected from the group consisting of anemia related to rheumatoid arthritis, anemia of infection and chronic inflammatory diseases, iron deficiency anemia, autoimmune hemolytic anemia, myelophthisic anemia, aplastic anemia, hypoplastic anemia, pure red cell aplasia, anemia associated with renal failure or endocrine disorders, megaloblastic anemias, defects in heme or globin synthesis, sickle-cell anemia, sideroblastic anemia, anemia associated with chronic infections, and myelophthisic anemias.

Salfeld et al (WO 97/29131) disclose a method of treating a patient with rheumatoid arthritis with human anti-TNFα antibodies that dissociates from human TNFα with a $K_d$ of 1 x $10^{-8}$ M or less and a $K_{off}$ rate constant of 1 x $10^{-3}$ $s^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an $IC_{50}$ of 1 x $10^{-7}$ M or less. Salfeld et al. do not teach or suggest a method of treating a patient with anemia with a therapeutically effective amount of a human antibody, or an antigen-binding fragment thereof, to the subject, wherein the antibody dissociates from human TNFα with a $K_d$ of 1 x $10^{-8}$ M or less and a $K_{off}$ rate constant of 1 x $10^{-3}$ $s^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an $IC_{50}$ of 1 x $10^{-7}$ M or less, such that the anemia is treated.

The Examiner cites http://www.emedicinehealth.com/rheumatoid_arthritis/article_em.html and asserts that anemia is a common complication of patients with rheumatoid arthritis, and therefore treating rheumatoid arthritis with an anti-TNFα antibody would necessarily treat anemia associated with rheumatoid arthritis. Anemia is a separate and distinct disorder. As disclosed in the specification as filed (see page 9, lines 3-12), anemia can develop as a result of another disease, such as chronic infections and inflammatory disease. Although the primary disease is treated with a particular therapeutic agent, there is no expectation that the same therapeutic agent will be efficacious in the treatment of anemia associated with that primary disease. Accordingly, if a patient with rheumatoid arthritis already presents with anemia, it does not necessarily follow that anemia will be treated by the

antibody, or antigen binding fragment thereof, of the claimed method, just because the rheumatoid arthritis is treated.

This is further evidenced by the fact that, each indication for which the drug may be promoted requires separate regulatory approval. Although a drug may be approved for a particular indication, separate regulatory approval is required for Abbott Laboratories to promote the use of the drug for additional indications, even ones that are associated with the primary disease. Accordingly, D2E7/HUMIRA cannot be sold for treating anemia.

Salfeld et al (WO 97/29131) does not teach or suggest each and every element of the present invention either expressly or inherently; i.e., anemia in a patient by administering a therapeutically effective amount of a human antibody, or an antigen-binding fragment thereof, to the subject, wherein the antibody dissociates from human TNFα with a $K_d$ of 1 x $10^{-8}$ M or less and a $K_{off}$ rate constant of 1 x $10^{-3}$ $s^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an $IC_{50}$ of 1 x $10^{-7}$ M or less, such that the anemia is treated. Because the cited reference does not teach or suggest the claimed methods of the invention, it fails to anticipate Applicants' invention.

In view of the foregoing remarks, Applicants submit the present invention as claimed is patentable over Salfeld et al (WO 97/29131) as evidenced by http://www.emedicinehealth.com/rheumatoid_arthritis/article_em.html. Applicants therefore respectfully request withdrawal of the rejection of claims 1-11 under 35 USC §102(b).

***Claim rejections under 35 USC §102(e)***

In the Office Action, at page 15, the Examiner has rejected claims 1-11, under 35 USC §102(e) as being anticipated by Salfeld et al (US Patent 6,509,015 B1) in view of http://www.emedicinehealth.com/rheumatoid_arthritis/article_em.html. The Examiner asserts that Salfeld et al., teach a method of treating rheumatoid arthritis, and since anemia is a common complication of rheumatoid arthritis, treatment of rheumatoid arthritis would necessarily treat anemia related to rheumatoid arthritis and thus Salfeld anticipates Applicants' claimed invention. Applicants respectfully disagree

Salfeld et al (US Patent 6,509,015 B1) disclose a method of treating a patient with rheumatoid arthritis with anti-TNFα antibodies. Salfeld et al. do not teach or suggest a method of treating a patient with anemia with a therapeutically effective amount of a human antibody, or an antigen-binding fragment thereof, to the subject, wherein the antibody dissociates from human TNFα with a $K_d$ of 1 x $10^{-8}$ M or

less and a $K_{off}$ rate constant of 1 x $10^{-3}$ $s^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an $IC_{50}$ of 1 x $10^{-7}$ M or less, such that the anemia is treated. The Examiner cites http://www.emedicinehealth.com/rheumatoid_arthritis/article_em.html and asserts that anemia is a common complication of patients with rheumatoid arthritis, and therefore treating rheumatoid arthritis with an anti-TNFα antibody would necessarily treat anemia associated with rheumatoid arthritis. For reasons stated above in response to the rejection of claims 1-11 under 35 USC §102(b) Applicants respectfully submit that the cited reference does not teach or suggest the claimed methods of the invention, and it fails to anticipate Applicants' invention.

In view of the foregoing remarks, Applicants submit the present invention as claimed is patentable over Salfeld et al (US Patent 6,509,015 B1) as evidenced by http://www.emedicinehealth.com/rheumatoid_arthritis/article_em.html. Applicants therefore respectfully request withdrawal of the rejection of claims 1-11 under 35 USC §102(e).

***Claim rejections under 35 USC §102(b)***

In the Office Action, at page 17, the Examiner has rejected claims 1 and 3-11, under 35 USC §102(b) as being anticipated by Kempeni et al (Ann. Rheum. Dis., 58(Suppl I): 170-172, 1999) in view of http://www.emedicinehealth.com/rheumatoid_arthritis/article_em.html. The Examiner asserts that Kempeni et al., teach a method of treating rheumatoid arthritis with D2E7, and since anemia is a common complication of rheumatoid arthritis, treatment of rheumatoid arthritis would necessarily treat anemia related to rheumatoid arthritis and thus Kempeni anticipates Applicants' claimed invention. Applicants respectfully disagree.

Applicants' invention is directed to a method of treating anemia in a subject comprising administering to a subject in need, a therapeutically effective amount of a TNFα antibody, wherein the antibody dissociates from human TNFα with a $K_d$ of 1 x $10^{-8}$ M or less and a $K_{off}$ rate constant of 1 x $10^{-3}$ $s^{-1}$ or less, such that anemia is treated. In a further embodiment the TNFα antibody is D2E7.

Kempeni et al (Ann. Rheum. Dis., 58(Suppl I): 170-172, 1999) disclose a method of treating a patient with rheumatoid arthritis with human anti-TNFα antibodies. Kempeni et al do not teach or suggest a method of treating a patient with anemia with a therapeutically effective amount of a human antibody, or an antigen-binding fragment thereof, to the subject, wherein the antibody dissociates from human TNFα with a $K_d$ of 1 x $10^{-8}$ M or less and a $K_{off}$ rate constant of 1 x $10^{-3}$ $s^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in*

*vitro* L929 assay with an $IC_{50}$ of 1 x $10^{-7}$ M or less, such that the anemia is treated. The Examiner cites http://www.emedicinehealth.com/rheumatoid_arthritis/article_em.html and asserts that anemia is a common complication of patients with rheumatoid arthritis, and therefore treating rheumatoid arthritis with an anti-TNFα antibody would necessarily treat anemia associated with rheumatoid arthritis. For reasons stated above in response to the rejection of claims 1-11 under 35 USC §102(b) Applicants respectfully submit that the cited reference does not teach or suggest the claimed methods of the invention, and it fails to anticipate Applicants' invention.

In view of the foregoing remarks, Applicants submit the present invention as claimed is patentable over Kempeni et al (Ann. Rheum. Dis., 58(Suppl I): 170-172, 1999) as evidenced by http://www.emedicinehealth.com/rheumatoid_arthritis/article_em.html. Applicants therefore respectfully request withdrawal of the rejection of claims 1and 3-11 under 35 USC §102(b).

***Double Patenting***

***Obviousness type double patenting***

In the Office Action, at page 18, claims 1-11 are rejected under the judicially created doctrine of obviousness double patenting as being unpatentable over claims 17 and 49 of U.S. Patent No. 6,509,015 B1. Applicants respectfully disagree.

As stated above on page 13, in response to the rejection of claims 1-11 under 35 USC §102(e) in view of U.S. Patent No. 6,509,015 B1, Applicants respectfully submit that the cited reference does not teach or suggest the claimed methods of the invention. Therefore, claims 1-11 are not obvious in view of the cited art. Accordingly, the rejection of claims 1-11 under the judicially created doctrine of obviousness double patenting being unpatentable over claims 17 and 49 of U.S. Patent No. 6,509,015, should be withdrawn.

In the Office Action, at page 20, claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness double patenting as being unpatentable over claims 1, 4-8 and 10-15 of co-pending U.S. Application No. 11/435,844. Applicants respectfully disagree.

Co-pending U.S. Application No. 11/435,844 claims a method of treating a patient with erosive polyarthritis with anti-TNFα antibodies. Co-pending U.S. Application No. 11/435,844 does not teach or suggest a method of treating a patient with anemia with a therapeutically effective amount of a human antibody, or an antigen-binding fragment thereof, to the subject, wherein the antibody dissociates from human TNFα with a $K_d$ of 1 x $10^{-8}$ M or less and a $K_{off}$ rate constant of 1 x $10^{-3}$ $s^{-1}$ or less, both

determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an $IC_{50}$ of 1 x $10^{-7}$ M or less, such that the anemia is treated.

As stated above, Anemia is a separate and distinct disorder. As disclosed in the specification as filed (see page 9, lines 3-12), anemia can develop as a result of another disease, such as chronic infections and inflammatory disease. Although the primary disease may be treated with a particular therapeutic agent, there is no expectation that the same therapeutic agent will be efficacious in the treatment of anemia associated with that primary disease. Accordingly, if a patient with erosive arthritis already presents with anemia, it does not necessarily follow that anemia will be treated by the antibody, or antigen binding fragment thereof, of the claimed method, just because the erosive arthritis is treated.

In view of the foregoing, claims 1-11 are not obvious in view of the cited art. Accordingly, the rejection of claims 1-11 under the judicially created doctrine of obviousness double patenting being unpatentable over claims 1, 4-8 and 10-15 of co-pending U.S. Application No. 11/435,844, should be withdrawn.

In the Office Action, at page 22, claims 1-11 are rejected under the judicially created doctrine of obviousness double patenting as being unpatentable over claims 1-23, 58, 60-70 and 73-84 of co-pending U.S. Application No. 10/163,657. Applicants respectfully disagree.

Co-pending U.S. Application No. 10/163,657 claims a method of treating a patient with rheumatoid arthritis with a bi-weekly dose of human anti-TNFα antibodies. Co-pending U.S. Application 10/163,657 does not teach or suggest a method of treating a patient with anemia with a therapeutically effective amount of a human antibody, or an antigen-binding fragment thereof, to the subject, wherein the antibody dissociates from human TNFα with a $K_d$ of 1 x $10^{-8}$ M or less and a $K_{off}$ rate constant of 1 x $10^{-3}$ $s^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an $IC_{50}$ of 1 x $10^{-7}$ M or less, such that the anemia is treated.

As stated above, Anemia is a separate and distinct disorder. For reasons stated above, claims 1-11 are not obvious in view of the cited art. Accordingly, the rejection of claims 1-11 under the judicially created doctrine of obviousness double patenting being unpatentable over claims 1-23, 58, 60-70 and 73-84 of co-pending U.S. Application No. 10/163,657, should be withdrawn.

In the Office Action, at page 22, claims 1-11 are rejected under the judicially created doctrine of obviousness double patenting as being unpatentable over claims 15-19 of co-pending U.S. Application No. 11/233,252 in view of Salfeld et al (WO 97/29131). Applicants respectfully disagree.

Co-pending U.S. Application 11/233,252 claims a method of treating a patient with rheumatoid arthritis and other diseases, but not anemia, with anti-TNFα antibodies. Co-pending U.S. Application 11/233,252 does not teach or suggest a method of treating a patient with anemia with a therapeutically effective amount of a human antibody, or an antigen-binding fragment thereof, to the subject, wherein the antibody dissociates from human TNFα with a $K_d$ of 1 x $10^{-8}$ M or less and a $K_{off}$ rate constant of 1 x $10^{-3}$ $s^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an $IC_{50}$ of 1 x $10^{-7}$ M or less, such that the anemia is treated.

As stated above, Anemia is a separate and distinct disorder. For reasons stated above, claims 1-11 are not obvious in view of the cited art. Accordingly, the rejection of claims 1-11 under the judicially created doctrine of obviousness double patenting being unpatentable over claims 15-19 of co-pending U.S. Application No. 11/233,252 in view of Salfeld et al (WO 97/29131), should be withdrawn.

In the Office Action, at page 22, claims 1-11 are rejected under the judicially created doctrine of obviousness double patenting as being unpatentable over claims of the following co-pending U.S. Applications; claims 1-29 of 10/622,205; claims 1-27 of 10/622,210; claims 1-26 of 10/622,683; claims 1-24 of 10/622,928; claims 1-14 of 10/622,932; claims 1-23 of 10/623,039; claims 1-24 of 10/623,065; claims 1-16 of 10/623,035; claims 1-34 of 10/623,076; claims 1-16 of 10/623,318; in view of Salfeld et al (WO 97/29131). Applicants respectfully disagree.

With the exception of co pending US application 10/622,932, none of the other cited co pending Applications claim a method of treating a patient with anemia, with a therapeutically effective amount of a human antibody, or an antigen-binding fragment thereof, to the subject, wherein the antibody dissociates from human TNFα with a $K_d$ of 1 x $10^{-8}$ M or less and a $K_{off}$ rate constant of 1 x $10^{-3}$ $s^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an $IC_{50}$ of 1 x $10^{-7}$ M or less, such that the anemia is treated.

As stated above, Anemia is a separate and distinct disorder. For reasons stated above, claims 1-11 are not obvious in view of the cited art with the exception of US application 10/622,932. Accordingly, the rejection of claims 1-11 under the judicially created doctrine of obviousness double patenting being unpatentable over claims 1-29 of 10/622,205; claims 1-27 of 10/622,210; claims 1-26 of 10/622,683; claims 1-24 of 10/622,928; claims 1-23 of 10/623,039; claims 1-24 of 10/623,065; claims 1-16 of 10/623,035; claims 1-34 of 10/623,076; claims 1-16 of 10/623,318; in view of Salfeld et al (WO 97/29131), should be withdrawn.

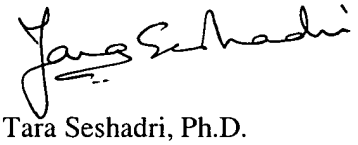
Upon determination of allowable subject matter in the instant application, Applicants will cancel claims directed to method of treating anemia from co-pending US application 10/622,932.

In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 1-11 under the judicially created doctrine of obviousness double patenting.

***Conclusion***

In view of the foregoing amendments and remarks, Applicants believe the rejections set forth in the Office Action dated 18 August 2006 have been avoided or overcome and consequently their application is in condition for allowance. Applicants, therefore, respectfully request reconsideration and withdrawal of the rejections, and allowance of the pending claims as amended.

Respectfully submitted,



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